U S A M M D A

United States Army
Medical Materiel Development Activity

"Developing Quality Medical Products for U.S. Forces"

2002 Annual Report
May 2003

United States Army
Medical Research and Materiel Command

U.S. ARMY MEDICAL MATERIEL DEVELOPMENT ACTIVITY
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Message From The Commander

The years pass quickly, and each one pauses to leave its mark; some years are remembered by a single defining moment, and some by a progression of events. The year 2002 was eventful for us at USAMMDA and actually represented the buildup towards a single defining moment, but we had not quite arrived there as the last seconds of the year ticked away.

During the early part of the year, USAMMDA continued to provide support and input to the MRMC working group writing contingency protocols. Significant advances continued to be made in many of our products: our excitement grew as the DEFTOS neared completion (this will be a major contribution to the AMEDD and the soldier). The development of the Needleless Injection Site was completed, the prototype One-Handed Tourniquet was provided to Special Operations Command, and the in-life portion of the Hepatitis E Vaccine field trial was completed, to name a few. In October, program management of our Chemical products was handed over to a new Program Executive Office (PEO), for Chem-Bio Defense.

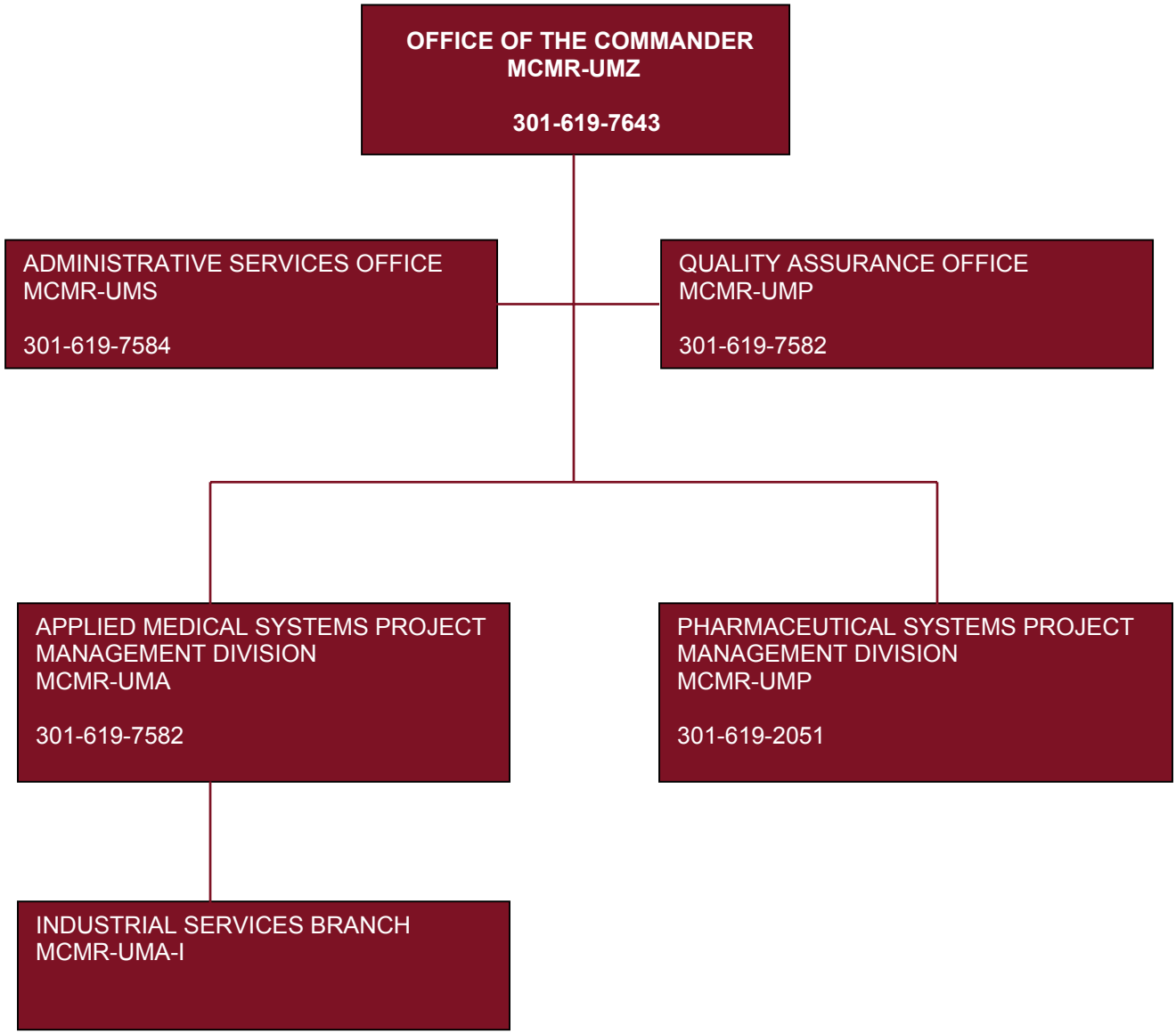
As we approached the end of the year, our focus was shifted heavily to preparation for the impending hostilities in Iraq and the Global War on Terrorism. We stood up a Special Medical Augmentation Response Team (SMART) for Investigational New Drugs (IND), which was task organized from several MRMC Subordinate Commands, plus support from MRMC Headquarters. We began the process of planning to support the deployed troops with investigational products (chem, bio and smallpox countermeasures). In December, we were notified by the FDA to immediately submit a New Drug Application for pyridostigmine bromide, basing our application on the newly enacted animal rule. Stay tuned for next year's annual report to find out how these dramas play out!

Finally, I would like to thank the staff of USAMMDA for the tremendous effort put forth over the past year. A true group of professionals, it is a privilege to work with you. And to the Commanders of our sister units – WRAIR, USAMRIID, USAMRICD, thank you for the support of the SMART-IND, for the sacrifices you have made in your research programs to the benefit of the U.S. Soldier, Sailor, Airman and Marine.

JEFFREY A. GERE
Colonel, MS
Commanding

USAMMDA Organization Chart

United States Army Medical Research and Materiel Command
United States Army Medical Materiel Development Activity



Our Mission

To protect and preserve the lives of America's sons and daughters by developing new drugs, vaccines and medical devices that enhance readiness, ensure the provision of the highest quality medical care to DoD, and maximize survival of medical casualties on the battlefield.

Our Vision

Military operations of the 21st Century will be more survivable because of USAMMDA initiatives.

- New drugs and vaccines that we developed will protect our personnel from the threats of infectious disease and chemical attack.
- Casualties will be evacuated in vehicles we developed.
- Our combat casualty care products will enhance far-forward medical care.

Lives that otherwise would be lost, will be saved because of the vision and dedication of USAMMDA employees.

Our Personnel

The U. S. Army Medical Materiel Development Activity (USAMMDA) experienced several personnel changes throughout 2002. We were faced with the loss of two civilian division chiefs within one month, along with several other personnel changes. One of our officers retired and three arrived. The Quality Assurance Office welcomed two civilians, while one of our Industrial Services Branch civilians accepted the retirement challenge. Due to heightened security requirements from 9/11, a new position was created to provide reception coverage at the front door. Entry is provided to persons who show proper identification. USAMMDA employees may access the building with key cards when the door is locked.

Matrixed support has continued to be provided to other organizations through a Memorandum of Agreement between the U.S Army Medical Research and Medical Command (USAMRMC) and the parent organizations. Five civilians are matrixed to the Chemical Biological Medical Systems Program (CBMS), formerly the Joint Vaccine Acquisition Program (JVAP), one civilian and two officers to the Medical Communications for Combat Casualty Care (MC-4), Enterprise Information Systems, two officers to the Telemedicine and Advanced Technology Research Center (TATRC), and one officer to the Joint Medical Operations - Telemedicine (JMOT).

The following table presents a comparison between 2001 and 2002 personnel strength. Overall, USAMMDA strength continues to vary between 56 and 62.

2001 Personnel Profile

Required	Authorized	Actual
72	39	62

2002 Personnel Profile

Required	Authorized	Actual
72	39	62

STRENGTH: As of 31 December 2001

	Military	Civilian	Contractors	Total
Required	18	44	10	72
Authorized	11	28	0	38
Actual	14	36	12	62

STRENGTH: As of 31 December 2002

	Military	Civilian	Contractors	Total
Required	18	47	10	75
Authorized	11	27	0	38
Actual	17	34	5	56

Fiscal Performance 2002

In-House: In FY02, USAMMDA's In-House fiscal execution of direct funds exceeded the USAMRMC obligation target by 2 percent and the disbursement target by 11 percent. The FY02 In-House direct funds included tech base funds received for quality assurance monitoring.

	In-House (Direct)		
	Allotment	Obligations	Disbursements
Fiscal 2002 Dollars ($000)	4,835	4,710	3,241
Target (%)		95	56
Actual (%)		97	67

In addition, USAMMDA In-House managed $5.6M in reimbursable funds in FY02. This included funds from the JVAP-BD and PM-MC4 offices for matrix support personnel, from the Marine Corps and the U.S. Army Security Assistance Command for the Joint Service Family of Decontamination Systems and the Reactive Skin Decontamination Lotion, from the DoD Washington Headquarters Services for the Malaria Rapid Diagnostic Device, and from the U. S. Army Medical Research Institute of Infectious Diseases (USAMRIID) for various task order services.

Program Wide: The FY02 laboratory and extramural programs exceeded the established targets by up to 5 percent for obligations, and by 12 to 15 percent for disbursements. Performance in the total Command-wide development program was 3 percent above the obligation target, and 14 percent above the target for disbursements. In addition, FY02 total program direct funds reflect a $10M increase over FY01, which is attributed mainly to an increase in combat casualty care funds. Total program execution exceeded FY01 actual disbursements by 19 percent, and fell short of FY01's obligation level by 1 percent. Fiscal execution performance at the project level is provided on the following page.

	Program-Wide (Direct)		
	Allotment	Obligations	Disbursements
Fiscal 2002 Dollars ($000)	34,104	33,533	23,740
Target (%)		95	56
Actual (%)		98	70

In FY02, USAMMDA also managed $7.9M of Congressional funds. FY02 Congressional funds were received for Future Medical Shelter, Life Support for Trauma And Transport, Blood Cell Washer, and Cartledge Infuser. In total, including direct, reimbursable, and Congressional funding, USAMMDA managed $47.7M of funds in FY02.

Fiscal 2002 Program Execution Table

DIRECT – ADVANCED DEVELOPMENT									
		PERCENT							
	Allotment	In-House		Lab		Extramural		Total	
Project	($000)	OBL	DISB	OBL	DISB	OBL	DISB	OBL	DISB
808	3,940	98	74	99	73	100	43	99	69
811	6,075	100	77	100	85	100	100	100	96
836	4,065	96	84	82	15	100	80	97	74
837	855	94	35	100	85	100	8	98	26
MC4	1828	100	66	99	78	100	83	100	80
Total 6.4	**16,763**	**97**	**72**	**98**	**71**	**100**	**85**	**99**	**79**
832	11,724	96	82	100	27	100	66	100	66
834	850	100	56	0	0	100	32	100	37
849	3178	97	44	62	47	94	56	89	52
MC5	1426	100	66	100	62	100	33	100	52
Total 6.5	**17,178**	**98**	**64**	**79**	**45**	**99**	**62**	**98**	**61**
Total Direct	**33,941**	**97**	**69**	**95**	**67**	**100**	**71**	**98**	**70**
REIMBURSABLE									
		PERCENT							
	Allotment	In-House		Lab		Extramural		Total	
Project	($000)	OBL	DISB	OBL	DISB	OBL	DISB	OBL	DISB
JVAP	320	100	100	0	0	0	0	100	100
Other Reimb	5,302	98	12	0	0	0	0	98	12
Total Reimb.	**5,622**	**98**	**17**	**0**	**0**	**0**	**0**	**98**	**17**
TOTAL PROGRAM MANAGED									
		PERCENT							
	Allotment	In-House		Lab		Extramural		Total	
Project	($000)	OBL	DISB	OBL	DISB	OBL	DISB	OBL	DISB
Total Program	**47,666**	**97**	**41**	**95**	**67**	**91**	**57**	**93**	**55**

Applied Medical Systems Project Management Division

Introduction

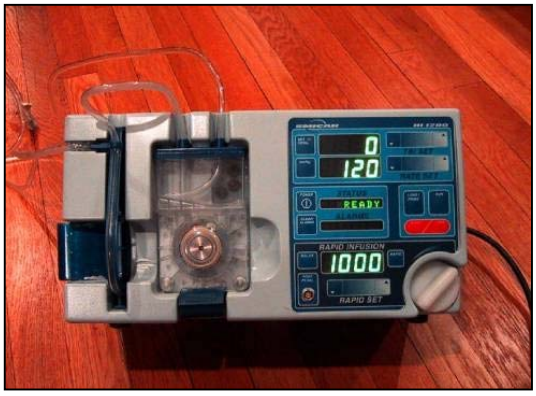
The Applied Medical Systems Project Management Division (AMSPMD) is a multidisciplinary team with broad mission capabilities for the advanced development of medical products used to sustain and support the warfighters. The team consists of both product managers and model makers, who have expertise in project management, engineering, fabrication, and technical testing. The product managers conduct analyses of functional requirements, develop and execute technical plans, and develop program strategies for all program components from pre-Milestone A through Full Rate Production. The product managers also direct program resources and defend program content and structure during science and acquisition forums. The focus for the Division has been on early involvement with products that are within the technology base resulting in streamlined development efforts by combining Milestones and transitioning medical products rapidly to the logistician for procurement and fielding. As a result of this emphasis, the Division is either developing strategies or monitoring research associated with many products. Examples include: Ceramic Oxygen Generator; Dental Field Treatment and Operating System; Future Medical Shelter System; Stryker Interim Armored Vehicle – Medical Variant; Hemostatic Dressing; Thawed Blood Processing System; and One-Handed Tourniquet.

Military Relevance

The AMSPMD designs, develops, and tests field medical equipment in support of battlefield combat casualties. The AMSPMD specializes in developing new and innovative breakthrough technology as well as adapting and hardening commercial off-the-shelf systems for joint military applications. For example, AMSPMD personnel were intimately involved with the Navy in the development of a Thawed Blood Processing System for far forward deglycerolization of frozen blood on board Naval ships which will extend the post-wash shelf-life from the current 1-day to 14 days. This will have a dramatic effect on the storage, logistics, and flexibility of processing and utilizing frozen blood.

Cartledge Infuser

The Cartledge Infuser (CI) is intended to allow a physician to normalize a patient's hemodynamic status. The CI is a variable rate infusion pump that allows a physician to replace blood volume at volume rates ranging from 20 ml per hour through 1200 ml per minute. A blood warming system is incorporated into the design and provides optimal blood warming at any flow rate. The CI operates on standard alternating electrical power, and is capable of battery operation for up to one hour. It weighs approximately 18 pounds, and is 14 inches wide, 8 inches high, and 8 inches deep.



The contract for the development of the CI was signed in September 2002. Design efforts are ongoing and Smisson-Cartledge, the contractor, selected Spartan, Inc., of Deland, FL, to finalize the design and produce the prototype system. A design review meeting at Spartan's facilities is scheduled for April 2003.

Ceramic Oxygen Generator

The Ceramic Oxygen Generator (COG) project is developing leading edge technology for the production of high purity, medical grade oxygen. This type of oxygen generator has an advantage over conventional methods such as pressure swing adsorption by generating very high purity oxygen without using any moving parts. This system uses a metal/ceramic membrane matrix to avoid the cracking and sealing problems that have been experienced by other developers attempting to commercialize COGs.

This year, a 3-liter per minute oxygen generator was demonstrated, and a new cell configuration was developed that will double the oxygen output per cell. The ceramic research is completed and the project is now focused on developing the packaging, controls, heat exchanger and batteries.

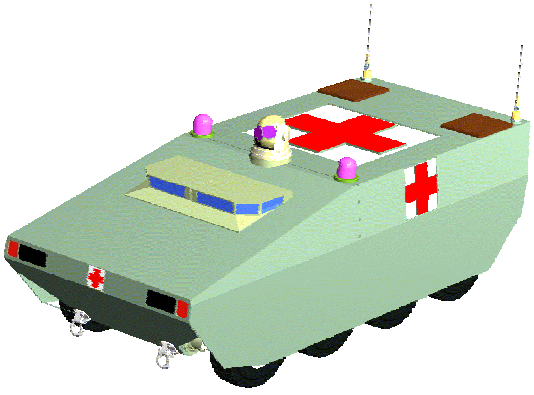
Dental Field Treatment And Operating System

The Dental Field Treatment and Operating System (DEFTOS) incorporates the latest technology to provide a modern, lightweight dental system for field operations. It reduces the need for compressed air and large power generator capacity in the field. The unit incorporates electric hand pieces, which produce superior torque during operation. A world-wide user evaluation of 20 units was completed. An analysis of the data indicated a user approval rate of about 85 percent, and provided several recommended changes. The units are being modified to incorporate these changes (e.g., 110-220 VAC, 50/60 Hz operation, improved vacuum, more comfortable foot switch). The modified units will be returned to field units for continued evaluation.

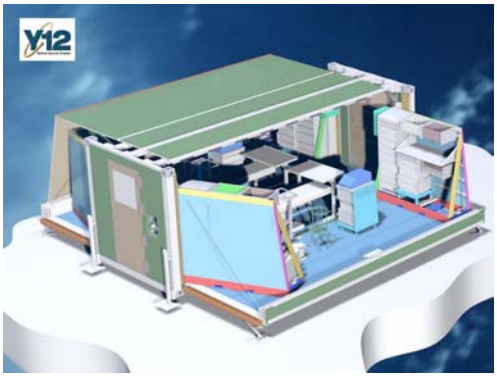
Future Combat System

The Future Combat System (FCS) - Medical Vehicle - Evacuation (MVE) and Medical Vehicle - Treatment (MVT) will function as the ground medical evacuation and treatment assets in the Unit of Action. Medical capability will include an automated litter lift system, on-board oxygen generation, suction, storage space for essential medical items and equipment, automated data management, plus the capacity to carry four litter patients or six ambulatory patients, and a crew of three.

USAMMDA participated in the FCS Medical Integrated Product Team, and provided input into the FCS Operational Requirements Document. The MV-E and MV-T are both recognized requirements in this document, and will be included in the 15 May 2003 Milestone B decision. We prepared the FCS Medical Vehicle performance specifications, and participated in the FCS Broad Industry Announcement proposal evaluation. We continue to be integrally involved in the UA and Unit of Employment concepts, and preparations for the transition to advanced development are ongoing.



Future Medical Shelter System



The Future Medical Shelter System (FMSS) is a multifaceted program designed to leverage Congressional funding to explore advanced rigid and soft-walled shelters for forward deployed healthcare providers. The scope of the FMSS program is (1) to develop a self-contained emergency response package for use by Forward Surgical Teams, and (2) to develop a replacement for the Deployable Medical Systems (DEPMEDS) operating room shelter. Both of these efforts consist of chemically/ biologically hardened International Standards Organization (ISO) containers with quick erect/strike times and integrated electrical, water, and medical packages. Both efforts also provide 1200 square feet of soft tentage as patient care wards. These efforts reduce the weight of comparable systems and enhance the transportability and deployability of forward medical care. Three development efforts are underway.

The Oak Ridge National Laboratory effort has been steadily progressing and achieved a final design that fully supports the concept proposed by the U.S. Army Medical Department Center and School (AMEDDC&S). It is anticipated that a prototype will be delivered in November 2003.

The Mobile Medical International Corporation contract was awarded in November 2002. This effort will focus on an ISO container-based replacement for the Forward Surgical Team (FST) that includes an integrated environmental control unit and generator. It is anticipated that a prototype will be delivered in 2005.

The EADS-Dornier effort is still in the concept stages. They are attempting to generate support among the Army and the Navy for a joint program that will develop a modified version of the German Trans-Hospital system. A formal proposal has yet to be received.

Field Operating Table Improvements

The current Field Operating Table used in DEPMEDS weighs nearly 800 pounds, and requires a large metal plate to distribute its weight on the operating room shelter floor. There is an existing Army design with a weight of 300 pounds that is stored in a compact container, but has rigidity problems and has had failures of the table elevation gear. This project will fix these problems making it a suitable replacement for the DEPMEDS table. An improved column lock was designed and fabricated this year. The cause of the gear failures is being investigated.

Field Sterilizer Improvement Device

The field sterilizer currently in use is a well-proven piece of equipment. One of the shortcomings has been its high water consumption; it uses 2½-gallons of water every time it sterilizes a load of materials. Additionally, the sterilizer does not have a vacuum system for removal of air during sterilization. This project will add a vacuum generator to the existing water recovery system, and fully field a Water Recovery System that reduces water consumption to less than a quart per operation.

The operational requirements for the Field Sterilizer Improvement Device were discussed with the combat developer, and preliminary design concepts were presented by potential contractors.

Hemostatic Dressing

The Hemostatic Dressing (HD) is intended to provide a revolutionary improvement in the control of severe life-threatening hemorrhage. The goal is to have a dressing that, when applied with direct pressure to or in the wound, will stop severe bleeding within four minutes. A contract with the American Red Cross (ARC) resulted in the submission of an Investigational New Drug (IND) Application and battlefield protocol to the Food and Drug Administration (FDA) this year.

The battlefield protocol was approved by the FDA and the ARC; and USAMRMC developed an informed consent procedure and other FDA-required documentation to make the HD available for use by Special Forces medics to treat casualties on the battlefield.

Interim AMEDD Tent Evaluation

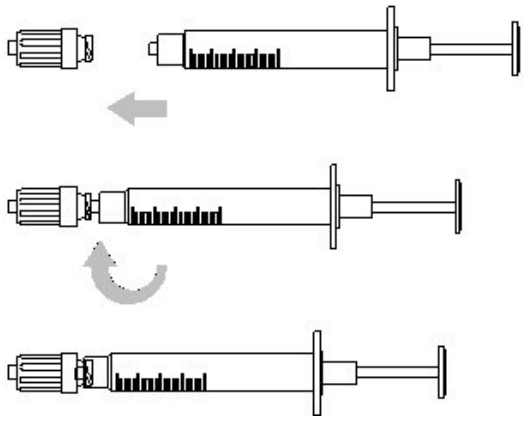
The Interim Army Medical Department Development (AMEDD) Tent Evaluation was intended to select an interim swap-out shelter for the DEPMEDS Combat Support Hospital (CSH), or re-establish confidence in the existing TEMPER tentage. In response to this tasking, USAMMDA worked closely with the AMEDDC&S and the U.S. Army Medical Department Board (AMEDDBD) on this project. Selection criteria were developed, an industry survey was conducted, potential candidate tent systems were down-selected, and a user evaluation was conducted at Camp Bullis, TX, from 2-13 December 2002. Final findings and recommendations are to be presented to the AMEDD senior leadership in 2003.

Life Support For Trauma And Transport

The Life Support for Trauma and Transport (LSTAT), developed by Integrated Medical Systems, Incorporated and the Walter Reed Army Institute of Research, is a computerized single-patient intensive care platform that maintains life support and stabilization of critical casualties in hospital, in other patient holding or treatment areas, and during patient transport. It has also been used as a surgical platform. The LSTAT allows a surgical and/or intensive care capability to be quickly set up almost anywhere. The LSTAT is designed to improve patient safety and reduce the number of highly trained nurses and respiratory therapists needed to monitor and treat intensive care patients. Since last year's annual report, 17 LSTATs have been fielded. The majority has been deployed in support of the war on terror. However, a small number has also been deployed in support of civilian and humanitarian health support operations including Operation BRAVA, an Army mission to provide surgical care to civilians in remote regions of Cambodia. Members of the surgical Special Medical Augmentation Response Team out of Tripler Army Medical Center performed this humanitarian mission. During Operation BRAVA, team members treated land-mine victims, victims of motor vehicle accidents, and patients with congenital orthopedic deformities. An LSTAT was also deployed to the Joint Trauma Training Center (located at the Ryder Trauma Center, University of Miami) where it is being used to train AMEDD clinicians. Further enhancement of the LSTAT system is underway to meet Objective Force requirements.

Needleless Injection Site

The Needleless Injection Site (NIS) concept is to design a standard "Needle-Free Injection Site" that is fully compatible with all syringes, Intravenous (IV) Infusion Administration Sets and IV Infusion Catheters. The NIS will incorporate all of the customary worldwide standards for Luer locking features that are found on both the male and female ends of the injection site, thereby allowing any syringe or IV infusion set to connect to the NIS without the need for a traditional stainless steel or plastic needle. This initiative will reduce the DoD's Operation and Support costs by reducing supply and inventory costs for several medical consumable items including stainless steel and plastic needles, decreasing medical waste disposal costs, and the potential for accidental needle sticks.



Standard Syringe with needle-free device.

Under the terms of the original U.S. Army Materiel Command's Commercial Operations and Support Savings Initiative (COSSI) agreement, development of this product was to be completed by December 2002. However, testing abnormalities delayed submission of the 510(k) to the FDA. In light of the testing abnormalities and the customer's desire for the product, the project completion date was extended until June 2003. All required testing was completed and verified during the last quarter, and the 510(k) documentation was submitted on 30 December 2002.

Non-Contact Respiration Monitor

The Non-Contact Respiration Monitor is a device for use by the medic to monitor the respiration of soldiers in Military Operational Protective Posture gear at a distance. It senses the flow of air entering the gas mask filter canister, and causes red or green light emitting diodes to signal the state of casualty breathing. This will be a new capability for the medic that will be particularly useful for triage in mass casualty nuclear, biological, and chemical environments. It will be lightweight, totally self-contained, and reliable in high noise and vibration environments such as medical evacuation helicopters. A patent disclosure and provisional patent were written this year. A first prototype was developed and initial technical testing was conducted. Future plans include integration of the device into Army gas masks.

One-Handed Tourniquet

The One-Handed Tourniquet (OHT) is to be carried by individual soldiers to enable a severely wounded casualty to stop the flow of blood in the field when assistance is not available. Ten thousand of the cinch-design OHTs have been procured of which half were provided to the Special Operations Command for user evaluation. Ten thousand additional OHTs are being procured by the U.S. Army Medical Materiel Agency (USAMMA) for contingency requirements. Initially, each Combat Medic (91W) will be provided three and each Combat Lifesaver will be provided two. A training package is being developed and user evaluation continues.

Portable Blood Refrigerator

The Portable Blood Refrigerator (PBR) is a lightweight, high efficiency refrigerator for chilling blood after collection, and storing blood during transport. A performance constraint of the current refrigerator is that it has a limited capability to chill blood from the collection temperature to the storage temperature.

Prototypes were fabricated and subjected to user testing, as well as temperature and vibration testing. The refrigerator was tested to an ambient temperature of 120°F and was able to maintain the correct temperature for blood storage in both the powered and un-powered modes. This item was transitioned to USAMMA for procurement this year.

Rotary Valve Pressure Swing Oxygen Generator

The Rotary Valve Pressure Swing Oxygen Generator (RVPSOG) is designed to replace the "D" cylinder for patient care and transport. The RVPSOG is a substantial simplification of existing pressure swing adsorption oxygen generator technology. The use of a rotary valve, driven directly by a small motor, eliminates complex valve and control systems used in conventional oxygen generators. Taking advantage of the reduced complexity reduces the weight and size of the oxygen generator and increases the efficiency of the generation process. This project will develop a portable device to meet the combat developers requirements for a point-of-use oxygen generator.

The contractor fabricated a prototype this year, and is working to reduce power consumption, weight and size and to increase the output of oxygen.

Special Medical Emergency Evacuation Device

The Special Medical Emergency Evacuation Device (SMEED) is a lightweight platform designed to quickly attach to a North Atlantic Treaty Organization litter, and support medical equipment. It was designed by SSG Eric Smeed, while stationed at the U.S. Army Institute of Surgical Research, to be used for medical evacuation of burn patients. The device is usually mounted over the feet of the patient, although it can be attached anywhere along the length of the litter. The platform has various universal fasteners so it can be configured in several ways, depending on the mission. It is specifically designed to accommodate all of the Patient Movement Items (PMI) in the Army inventory to include vital signs monitor, infusion pump, aspirator, D-cylinder oxygen tank, ventilator, defibrillator, and the flexibility to mount other medical devices as required.

The SMEED has the support of the Army combat developer, U.S. Air Force, the Marines and other users. The Army has identified it as a PMI, and for use in the Forward Surgical Teams. The Air Force granted Air Worthiness Release (AWR) this year, and is now receiving shipments of 125 SMEED units. The Marines have placed an order for 25 SMEEDs. Currently, the Army is awaiting the results of Army AWR testing prior to procurement.

Stryker - Medical Evacuation Vehicle

The Stryker - Medical Evacuation Vehicle (MEV) will function as the medical evacuation variant of the Stryker Armored Vehicle platform for the Stryker Brigade Combat Team. Medical capability includes an automated litter lift system, on-board oxygen, suction, storage space for essential medical items and equipment, plus the capacity to carry four litter patients or six ambulatory patients, and a crew of three.

USAMMDA provided expert technical and integration support to assist in the development of this product. This year the initial design was completed, and 27 units were produced. Test articles were provided to both Aberdeen and Yuma Test Centers

and are currently undergoing testing. We are working closely with all concerned players to resolve any issues prior to Initial Operational Test and Evaluation in June 2003.

Thawed Blood Processing System

The Thawed Blood Processing System (TBPS) consists of a blood processor and related components that will replace the existing frozen blood system. The current system does not meet military requirements because it is labor-intensive, limits production to 1-blood unit per hour per technician, and limits shelf life of processed thawed blood to only one day. The new system is an automated, closed-loop sterile blood-processing system capable of increasing production and shelf life (of processed blood) from the current 1-day to 14-days. The TBPS also includes: a bar code reader for automated data collection; a newly designed dry thawing device to reduce thaw time from the current 50 minutes in a conventional water bath to less than 10 minutes; and a new blood bag to eliminate the current 20 percent to 50 percent leakage rate. The TBPS processing device is a compact tabletop design.

Considerable work was done this year to improve the quality system for manufacturing. This includes contracting with a laboratory that is Good Manufacturing Practice certified, and experienced with manufacturing blood filters that meet FDA requirements, including necessary documentation. Preparations were made to conduct additional testing that was requested by the FDA. Disposables were produced and sterilized, and additional *in vitro* tests at three selected laboratories are about to be initiated.

Ventilatory Assist Device

The Ventilatory Assist Device (VAD) is an anesthesia delivery system consisting of an anesthesia apparatus, ventilator, and patient ventilator circuit. The VAD will be used to anesthetize patients during surgical procedures at Forward Surgical Team (FST) locations. The VAD will eliminate the need to ventilate the patient during surgery by hand bagging by the anesthesia provider. Manually ventilating a patient is very labor-intensive and reduces the number of surgical procedures that can be performed. It will be compatible with low-pressure oxygen sources such as oxygen concentrators. The use of the VAD will ensure proper patient ventilation during surgery.

The VAD was validated for use with oxygen concentrators this year, and has received clearance for marketing by the FDA. Preparations were made to evaluate the suitability of the VAD for use at various FST sites in 2003.

Industrial Services Branch

Introduction

The Industrial Services Branch (ISB), Applied Medical Systems Project Management Division, is a small team of craftsmen model makers possessing at least two trade skills who design, develop drawing packages, and rapidly prototype medical equipment in support of the U.S. Army Medical Research and Materiel Command. The ISB is capable of rapidly prototyping medical devices in a range of scales and variety of materials, and can also harden commercial off-the-shelf equipment for use in a field environment.

Major Accomplishments

The ISB designed, modeled, and fabricated a variety of medical items this year, including a Miniaturized Portable Ventilatory System, Non-Contact Respiration Monitor, and components of the Field Operating Table. The ISB also supported the Command and the Fort Detrick Community in numerous other projects to include the fabrication of parts and mounting of weapons onto vehicles following the 11 September 2001 terrorist attacks.

Miniaturized Portable Ventilatory System

In the wake of the 9/11 terrorist attacks, a collaborative effort between the U.S. Army Center for Environmental Health Research and the ISB ensued to design and fabricate a miniaturized bio-monitoring device. In a period of three months, the institutional science, engineering, modeling, and fabrication skills and capabilities of these two organizations were brought together to successfully design and build the Miniaturized Portable Ventilatory System. The purpose of this device is to provide a new sensor technology for the detection of active and toxic agents in water supplies. The unit greatly reduces the logistical footprint for performing ventilatory bio-monitoring, and also adds a function of portability that has never been realized for ventilatory bio-monitoring.

Once the general redesign was complete, drawings were produced and nine units were fabricated. During the production process, the research and development continued, and the design went through further testing that indicated the need for other improvements. One such improvement was that of foldable bracing that enables the unit to withstand extreme side impact loading. Finally, additional units were fabricated and a data package developed encompassing all of the latest improvements.

Pharmaceutical Systems

Introduction

The Pharmaceutical Systems Project Management Division (PSPMD) centrally manages the development and acquisition of pharmaceutical and biological products (drugs, vaccines, toxoids), related drug delivery systems (e.g., autoinjectors), resuscitative fluids, and skin protectants. These products are fielded as preventive, protective and therapeutic modalities for use against infectious diseases, chemical and biological warfare threats, and for the treatment of combat casualties. Product Managers leverage domestic and foreign medial technology to remedy deficiencies identified by the Combat Developer and monitor military, industrial, and university research projects for potential solutions to identified problems.

Military Relevance

U.S. Military Forces must be prepared to serve anywhere in the world against any threat. This could result not only in conventional injuries sustained during combat operations but exposure to chemical and biological warfare agents, as well as exposure to endemic diseases not commonly found in the United States. The development of products against these threats will help save lives, sustain the fighting Force and enhance return to duty.

Hepatitis E Virus Vaccine

The Hepatitis E Virus Vaccine (HEVV) consists of a purified polypeptide produced in insect cells infected with a recombinant baculovirus containing truncated hepatitis E virus (HEV) genomic sequences encoding the viral capsid antigen. The recombinant HEV protein is formulated with an aluminum salt adjuvant. The HEVV is designed to protect DoD personnel and their families from hepatic disease caused by infection with the HEVV.

A phase II, prospective, randomized, double-blind, placebo-controlled (vaccine placebo 1:1) field efficacy trial of the HEVV was started in Royal Nepal Army personnel in Kathmandu in 2001. The two thousand volunteers received either placebo or 20 micrograms of HEV recombinant protein at 0, 1 and 6 months. The volunteers are being followed for signs and symptoms of hepatitis for 24 months after the first dose. Completion of the trial is expected in late CY03. The lead laboratory is Walter Reed Army Institute of Research (WRAIR).

Human Immunodeficiency Virus Vaccines

The Human Immunodeficiency Virus Vaccines (HIVV) consists of two components: a prime component using gene-based/vectored technology (recombinant canary-pox virus expressing HIV genes) designed to induce cellular immunity against the HIV subtype E, and a boost component using recombinant technology designed to induce humoral immunity against envelope proteins of the HIV subtype E. The HIVVs are designed to protect DoD personnel against disease caused by infection with the HIV subtype E.

Phase I and II trials designed to determine the safety and immunogenicity of vaccine combinations that use the canary-pox HIV recombinant prime and a recombinant gp120 or gp160 envelope protein boost were carried out in Thailand during 1999-2001. Immunogenicity data from the trials showed that the canary-pox HIV recombinant, in combination with the variety of subunit envelope boosts, induces immune responses that are consistent with pre-defined immunogenicity targets for advancement to a phase III trial. Preparations for a phase III trial using the HIV-1 recombinant canary-pox vectored vaccine prime and a recombinant gp120 B/E envelope protein boost in HIV-uninfected Thai adults are underway. The expected start date of the phase III trial is late calendar year 2003. The lead laboratory is WRAIR.

Campylobacter Vaccine

The *Campylobacter* Vaccine is a killed, whole-cell oral vaccine adjuvanted with LT toxin designed for administration to military personnel prior to deployment to areas (worldwide) where *Campylobacter* bacteria are known to be the cause of acute diarrhea.

During CY02, a Phase II safety and immunogenicity study was conducted in U.S. adult volunteers to further evaluate a new four-dose, short interval regimen for vaccine administration. An expanded Phase II study in U.S. volunteers is planned in CY03 to gather more extensive information on the safety and immunogenicity of the four-dose, short interval regimen. The lead laboratory is Naval Medical Research Center (NMRC).

Combined Camouflage Face Paint

The Combined Camouflage Face Paint (CCFP) now offers more than simple concealment. The CCFP formulations, in compact and/or stick-type containers, will be a U.S. Environmental Protection Agency registered blend of face paint with DEET insect repellent to provide a minimum of 8 hours of protection against biting insects. Inclusion of insect repellent protection will reduce nuisance factors, diseases due to biting insects (e.g., malaria and dengue fever) and position disclosure due to movement in attempts to avoid the insects. All CCFP formulations will be used by individual soldiers for protection against biting insects, protection against detection by night vision goggles (the face paint reduces a soldier's near-infrared signature) and for blending into the environment in all military missions.

During CY02, final packaging and color specifications were developed for the new five-color CCFP compact. The new CCFP is packaged in a compact container with a mirror on top and compartments on the bottom to provide for 20 applications of the loam, green, and sand colors, and 10 applications of black and white colors. A new multi-year Cooperative Agreement was awarded to an Industry Partner to provide CCFP performance in stick-type dispensers. The lead laboratory for efficacy is WRAIR. The lead laboratory for camouflage is Natick Soldier Center.

Dengue Tetravalent Vaccine

The dengue tetravalent vaccine (DTV) is a live-attenuated virus vaccine for prevention of dengue fever. The DTV contains all four monovalent serotypes grown in fetal Rhesus lung (FRhL) cell culture.

In CY02, a Phase I vaccine trial was conducted to evaluate the safety and immunogenicity of the most promising DTV formulation. A human dengue challenge model was established to directly determine vaccine efficacy. Preliminary results indicated that previously DTV vaccinated volunteers, with adequate neutralizing antibody titers, were protected against dengue fever symptoms when challenged with near wild-type dengue virus. The lead laboratory is WRAIR.

ETEC Whole Cell, Recombinant B Subunit Vaccine

The ETEC is a vaccine composed of killed whole cell *Escherichia coli* (*E. coli*) plus the B subunit of cholera toxin produced by recombinant technology to protect U.S. Forces deployed worldwide against severe diarrhea and fever caused by enterotoxigenic *E. coli*. The vaccine is manufactured by SBL Vaccin, a subsidiary of PowderJect, Inc. The lead laboratory is NMRC.

In CY02, the Phase III efficacy studies in Egyptian infants and in Israeli Defence Force volunteers were completed. Analyses of the data generated by these studies are underway currently. No further clinical studies are planned for CY03.

Lethal Ovitrap For Dengue Vectors

This is a female Aedes Aegypti mosquito engorged with blood while feeding. Dengue viruses are transmitted during the feeding process.

The Lethal Ovitrap for Dengue Vectors (LODV) is used to kill the dengue virus primary vector mosquito (*Aedes aegypti)* that normally breeds in artificial containers. One of the most basic, non-chemical, vector control measures for *Aedes aegypti* populations is source reduction of potential breeding sites. The LODV is a simple device comprised of a 473 milliliter black plastic cup filled with water to within 2.5 centimeters (cm) of the brim, and an attached 2.5 x 11 cm red velour strip treated with a pyrethroid insecticide. The LODV is a device that breaks the dengue life cycle by killing the dengue virus carrying egg-laying female mosquitoes and their larvae at the breeding site. The LODV will be placed in and around base camps to protect troops in dengue threat areas. Dengue Fever (DF) is endemic in many tropical regions of the world where military personnel are stationed or may deploy. Worldwide, fifty to one hundred million people are infected with dengue annually, with an estimated two million cases of Dengue Hemorrhagic Fever (DHF) and thirty-five thousand deaths. Dengue epidemics are explosive, with the potential to rapidly incapacitate large numbers of personnel requiring prolonged hospitalization, and convalescence lasting several weeks.

Field trials in dengue threat areas failed to clearly and consistently demonstrate effectiveness of the LODV presumably due to several unresolved technical issues, leading the Product Manager to recommend termination of advanced development. The lead laboratory is WRAIR.

Leishmania Skin Test

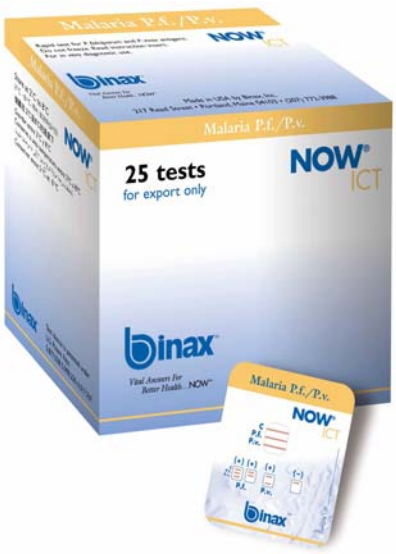
The *Leishmania tropica* Skin Test will be an intradermal test for the screening of U.S. Service members who may have been exposed to *Leishmania* parasites after deployment to leishmaniasis endemic areas of Southwest Asia/Africa. The skin test will stimulate a delayed type hypersensitivity response (seen as a small bump of 5mm or greater) in individuals previously infected with *Leishmania*. The disease leishmaniasis is caused by protozoan parasites transmitted to humans from the bite of an infected sandfly. More than 400,000 new cases of human leishmaniasis are reported annually in the world.

Skin lesion from a person with cutaneous leishmaniasis (CDC/Dr. D.S. Martin).

During CY02, our commercial development and production partner validated their current Good Manufacturing Practices production facility for the *Leishmania* Skin Test. Additional manufacturing information was submitted to the FDA on the new Investigational New Drug (IND) for the *L. mexicana* Skin Test, a pre-planned product improvement program to expand the diagnostic capability to detect exposure to *Leishmania* species from Latin American countries. A Phase I safety trial was conducted for this *L. mexicana* Skin Test. A protocol was developed for a Phase II potency, sensitivity and dose ranging study of the two WRAIR-manufactured skin tests made from *L. tropica* and *L mexicana* promastigotes. The lead laboratory is WRAIR.

Malaria Rapid Diagnostic Device

The Malaria Rapid Diagnostic Device (MRDD) will be a handheld, disposable device to rapidly detect malaria parasites in blood samples of patients displaying symptoms of malaria. The MRDD will not require the use of additional equipment to analyze appropriate clinical specimens. The MRDD will facilitate the early diagnosis of malaria infection and prompt medical intervention.



During CY02, a statistical analysis was initiated to evaluate performance of the MRDD from the data collected from clinical studies conducted in Peru and Thailand. Also during CY02, funding was secured from the DoD Commercial Operations & Support Savings Initiative (COSSI) Program to complete the MRDD development and obtain FDA approval. These COSSI funds are for leveraging private sector research and development by inserting leading-edge commercial malaria

diagnostic technology into fielded military systems with the goal to reduce operations and support costs. Continued close liaison with our diagnostic medical device manufacturer and the FDA has helped to minimize programmatic risks. The lead laboratory is WRAIR.

Topical Antileishmanial Drug, Paromomycin/Gentamycin

Soldiers who contract cutaneous leishmaniasis are currently evacuated to the Walter Reed Army Medical Center and treated under an IND application with Pentostam®, which is administered intravenously for 28 days. This extended treatment regimen possesses undesirable side effects, requires hospitalization, and is expensive. The Topical Antileishmanial Drug is a topical ointment made from two aminoglycosides antibiotics, 15 percent paromomycin sulfate and 0.5 percent gentamycin sulfate, in an aquaphilic base for the topical treatment of cutaneous leishmaniasis. This drug could replace Pentostam® for the treatment of the cutaneous form of leishmaniasis.

A Phase II clinical trial protocol is awaiting approval by the Human Subjects Research Review Board. This protocol is being performed in cooperation with the Institut Pasteur – Paris and Tunisia against Old World Leishmania. This study is planned to start in March 2003 to continue until July 2004. The lead laboratory is WRAIR.

Malaria Recombinant Vaccine With Adjuvant Combinations (RTS,S)

RTS,S vaccine consists of recombinantly engineered immunogenic fractions of the malaria sporozoite surface coat co-expressed with protective epitopes from the hepatitis B surface antigen. During purification, these proteins self-assemble into particles that form the antigenic component of the vaccine. The vaccine is formulated in a liquid emulsion containing potent immunostimulants (designated as SBAS2) that dramatically enhances the immune response to the RTS,S particles. The vaccine is delivered by intramuscular injection to protect U.S. Forces from falciparum malaria. The vaccine is manufactured by GlaxoSmithKline Biologicals. The lead laboratory is WRAIR.

During CY02, the RTS,S vaccine was combined with a novel, proprietary adjuvant and the vaccine-adjuvant combination evaluated in preclinical animal studies. In CY03, a Phase I/IIa safety, immunogenicity and preliminary efficacy study in U.S. adult volunteers is planned.

Shigella Flexneri Vaccine (SC602)

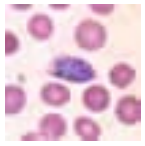
Shigella flexneri 2a vaccine (SC602) is a live, oral, attenuated vaccine developed at the Institut Pasteur in France and manufactured as a lyophilized product in the WRAIR pilot vaccine production facility under current Good Manufacturing Practices. The SC602 strain is attenuated by inactivation of the icsA gene in the invasive plasmid and inactivation of the iuc (aerobactin) gene in the chromosome. The mutations prevent

spread of the organism within the intestinal epithelium and diminish iron-binding capacity, but do not affect immunogenicity.

During CY02, planned Phase II safety and immunogenicity studies in U.S. adult volunteers could not be conducted because of the increased operational requirements necessitated by the terrorist attacks in New York and Washington D.C. A planned Phase II safety and immunogenicity trial in U.S. adult volunteers from the Multinational Observer Force in the Sinai Peninsula, Egypt, could not be conducted due to logistical and operational constraints at the field site. A Phase II safety and immunogenicity study in Israeli adult volunteers and adult household contacts is planned for CY03. The lead laboratory is WRAIR.

Antimalarial Drug, WR238605

WR238605 (Tafenoquine) is an 8-aminoquinoline that has demonstrated antimalarial potential in both pre-clinical and clinical studies. While it has demonstrated potential both as a prophylactic and treatment drug, it is being developed first for the prophylaxis indication.

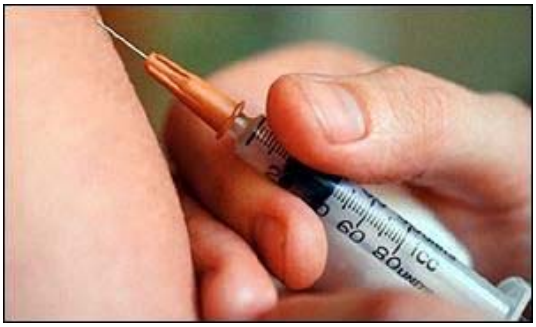


Schizonts of *P. ovale* in a thin blood smear.

Additional pre-clinical toxicity studies and review of previous data confirmed that the renal toxicity findings were confined to male rats only. Female rats and both male and female mice were free of tumors when exposed to high doses of tafenoquine for two years, and repeat genotoxicity and lymphocyte studies were negative. In addition, follow-up examinations of Australian soldiers who received tafenoquine during deployment to East Timor as part of a Phase III trial demonstrated complete resolution, by one year after study completion, of the phospholipid deposits that occurred in the corneas of most of the tafenoquine recipients. These additional safety data were presented to the FDA in December, after which the FDA allowed the tafenoquine IND application to be re-activated effective 19 January 2003. Additional follow-up of a subset of Australian soldiers who had mild elevations of serum creatinine at study end has demonstrated no evidence of persistent renal toxicity in humans.

A new Phase I safety trial is planned that will closely examine normal volunteer subjects in a prospective fashion for any evidence of effects on renal function or visual function due to administration of tafenoquine. This trial, which will commence in the spring of 2003, will be carried out at the Uniformed Services University of the Health Sciences. Positive study results will allow the re-starting of Phase III clinical trials. Threat conditions continue to have an impact on Phase III study site availability and access, and alternative sites are being investigated for suitability for these trials. The lead laboratory is WRAIR.

Tick-Borne Encephalitis Vaccine



The Tick-Borne Encephalitis (TBE) vaccine is an inactivated viral vaccine for the prevention of TBE. TBE is endemic in several European countries, Russia, and China. The disease has a 7-14 day incubation period, typically followed by 4 days of fever. A small percentage of those with TBE will experience a meningo-encephalitis requiring hospitalization and prolonged recovery. In general, mortality is 1-2 percent, but can be as high as 23 percent in the Far East. The vaccine is 70 percent effective following the first dose, 95 percent following the second dose and >99 percent following the third dose.

During CY02, a COSSI proposal, needed to conduct the requisite clinical trials in support of the FDA licensure, was not funded. The Product Manager will continue to seek alternate funding sources.

Antidote Treatment - Nerve Agent, Autoinjector

Formerly Known As The Multichambered Autoinjector (MA)

The Antidote Treatment - Nerve Agent, Autoinjector (ATNAA) is a simple, reliable system for self-administration of multiple chemical warfare agent antidotes from a single autoinjector. The ATNAA is a cylindrically shaped device with a length of 18 cm and a diameter of 2.5 cm. Exposed needle length does not extend more than 2.5 cm, and the overall weight is 55 grams. The ATNAA contains atropine and 2-pralidoxime in the same autoinjector but in different chambers and will deliver both products through a single needle.

The ATNAA individual external packaging passed the Initial Operational Test and Evaluation (IOT&E). Transition Planning and Tracking Group meetings between the Services, Army Office of The Surgeon General, and the U.S. Army Medical Materiel Agency took place to assure a smooth transition to full rate production. A successful Full Rate Production In-Process Review was held transitioning the ATNAA to production and deployment. Validation batches for the new automated production line were produced.

Identification of degradants in the 3-year stability samples of ATNAAs was completed and a Supplement to the FDA requesting a 3-year stability for ATNAAs was prepared.

Assay For Detection Of Plasmodium In Mosquitoes

A requirement exists to develop a device to rapidly detect *Plasmodium vivax* in mosquitoes. The Assay For Detection Of Plasmodium In Mosquitoes (ADPM) was developed with specific reagents and adapted to a wicking assay technology. The analytical methodology of the detection device is based on enzyme-linked immunosorbent assays (ELISA), colloidal gold labeling in the capture reagents, and application of the assay elements to nitrocellulose strips. The field usable assay will assist preventive medicine professionals in performing threat assessments and vector control operations. Assay results are essential to support determination of appropriate preventive countermeasures to prevent the impact of malaria, performance degradation, and death to armed members exposed to *Plasmodium vivax*.

The Milestone Decision Authority approved the Acquisition Decision Memorandum for the Correspondence Full Rate Production In-Process Review to advance the Program to the Production and Deployment Phase. The ADPM Kits were deployed and used in the Afghanistan Military Action.

Soman Nerve Agent Pretreatment Pyridostigmine

Pyridostigmine Bromide (PB) is an oral pretreatment, which will enhance the effectiveness of antidotal atropine/2-pralidoxime chloride treatment against nerve agent poisoning by soman.

CY02 efforts concentrated on initiating and coordinating studies to address the FDA's questions on the PB NDA: a) a protocol for a critical clinical study to evaluate the ability of PB to protect excised human muscle against soman-induced intoxication was reviewed by the FDA and a Subject Matter Expert Panel was formed to develop strategy to address FDA's comments; b) a Guinea Pig Study, designed to answer FDA's questions about adequacy of the surrogate marker, continued its in-life phase; c) a protocol for an FDA-mandated study to evaluate the ability of PB to protect excised monkey muscle against soman-induced intoxication was prepared; d) the clinical study to address the adequacy of PB to protect enzymes in human blood was conducted and assays for acetylcholinesterase levels were started; and e) Integrated Project Team Meetings were held to assure the research efforts were as productive as possible. On 19 December 2002, the FDA directed the sponsor to submit an NDA as fast as possible, under the new Animal Rule.

Skin Exposure Reduction Paste Against Chemical Warfare Agents

The Skin Exposure Reduction Paste Against Chemical Warfare Agents (SERPACWA) is a paste containing chemically inert perfluorinated polymers. When used in conjunction with the M291 Skin Decontaminating Kit or Mission-Oriented Protective Posture Gear, the SERPACWA will prevent or significantly reduce the toxicity following percutaneous exposure to Chemical Warfare Agents (CWA). The FDA approved the NDA for SERPACWA on 17 February 2000. The Milestone III In-Process Review was conducted on 12 September 2000. The SERPACWA is now in Production and Deployment phase.

A post-approval, Phase IV study was conducted and showed the SERPACWA remains wholly protective after eight hours of wear under the Battle Dress Uniform (BDU) and Battle Dress Outergarment (BDO). A transfer study showed that washing or wiping hands following SERPACWA application prevented SERPACWA transfer to cigarettes. Other post-approval studies are near completion: a study to determine whether the Service Member can understand the use instructions and apply the SERPACWA on the skin correctly; an animal study to determine the toxicity of fumes from burning one of the ingredients of SERPACWA; and a laboratory study to determine whether SERPACWA is compatible with the fabric of BDU and BDO.

The AMEDDC&S approved an Interim Doctrine of Use. The Training Support Package is being revised.

The scale-up manufacturing capability and packaging operations were validated.

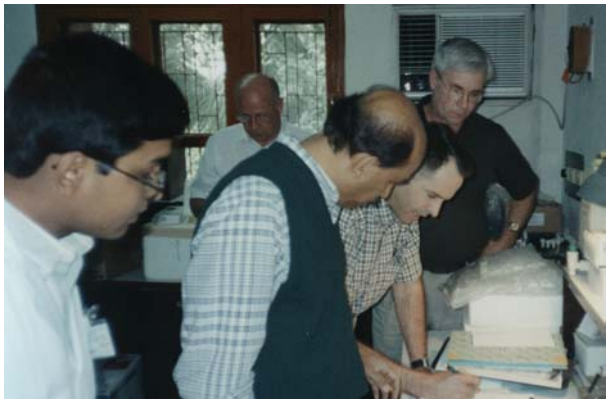
Quality Assurance

Major Accomplishments

The Quality Assurance Office, like the rest of the U.S. Army, has had to cope with changing priorities and contingency planning in the face of international developments. One Department of the Army civilian was added to the staff, and one contractor converted to a Government Service position, giving added strength and stability to the staff.

Bengalee infants with their mothers, wait for the Shigella vaccine.

The QAO has maintained its focus on Good Clinical Practice (GCP) monitoring of Army-sponsored protocols or protocols in which the Army is an active partner, now nearly sixty in number. The draft GCP checklist developed in CY01 has been finalized and implemented, with excellent feedback from monitors, Product Managers and study staff. The QAO has actively assisted with contingency protocols and emergency treatment protocols, proactively putting into place monitoring procedures. More specifically, the QAO monitored pivotal studies requested by the FDA in order to approve use of Pyridostigmine Bromide as a prophylactic drug to protect against the effects of nerve agents. An additional tasking involved monitoring four post-marketing studies at the request of the FDA for SERPACWA. USAMMDA's QAO has been an integral part of ongoing monitoring of emergency treatment protocols in place as part of the renewed program for immunization of military personnel against smallpox.



Monitoring of Shigella vaccine study in Bangladesh

Building on last year's expansion into Good Manufacturing Practice (GMP) or Good Laboratory Practice (GLP) areas, the QAO staff visited updated facilities for producing the Chitosan Bandage (a hemostatic agent) as part of revalidation of the facilities, equipment and production. The QAO staff also traveled to Melbourne, Australia, for GMP audit facilities producing a blood-product derived hemostatic dressing intended to stabilize life-threatening traumatic injuries.

QAO's commitment to excellence encompasses study monitoring of test sites located worldwide.

The QAO maintains a brisk, vigilant monitoring program to assure the safety of volunteer subjects and the integrity of scientific data. To accomplish this, the staff traveled extensively in the United States and overseas. In addition to frequent local visits to WRAIR and USAMRIID, staff members conducted monitoring visits to Phoenix, AZ; Portland, OR; Lincoln, NE; Natick, MA; San Diego, CA; and other stateside locations. Overseas monitoring visits took place in Nepal, Peru, Egypt, Ghana, Kenya, Australia, Thailand, France, Tunisia, England, and Korea.

Katmandu version of the corner drug store.

Street view from the window of the Abu Homos ETEC study site in Egypt.

As the world at large and the military scientific research community grow ever more complex, USAMMDA's QAO is ready to contribute and assist in the development of quality drugs, vaccines and medical devices for soldiers, wherever and whenever our assistance is needed.

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